# An Update on the Treatment of the Cutaneous Manifestations of Systemic Sclerosis

## The Dermatologist's Point of View

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## ABSTRACT

Systemic sclerosis is a connective tissue disorder that affects multiple organs. Although the initial symptoms of the disease are vascular, skin involvement is almost universally present in patients with systemic sclerosis. The presence of Raynaud's phenomenon, progressive thickening of the skin, digital ulcers, and calcinosis all correlate proportionally with disease severity. Since no treatment is available to completely prevent the natural course of the disease, emphasis is often placed on managing symptoms and complications. In this review, the authors focus on the management of each one of the skin manifestations seen in systemic sclerosis, as the dermatologist may facilitate the early recognition and treatment of these complications. (*J Clin Aesthet Dermatol.* 2012;5(7):33–43.)

Systemic sclerosis (SSc) is a rare and progressive connective tissue disease of a multifaceted origin that is more common among women in the third to fifth decades of life and is rare in children. Clinical symptoms of overt disease include peripheral and persistent microvascular vasoconstriction, swelling of the fingers, skin tightening, contractures of the fingers, polyarthralgia, and dysphagia. The most common initial symptoms and signs are vascular, such as Raynaud's phenomenon, which is often long-lasting, as well as insidious swelling of the distal extremities, followed by gradual thickening of the skin of the face and fingers with eventual skin ulceration.[1] The pathophysiology of SSc involves endothelial and vascular damage and the activation of fibroblasts; consequently, collagen and other extracellular matrix proteins are overproduced in almost all tissue.[2] In the skin, SSc is characterized by more compact collagen fibers and other extracellular matrix proteins in the reticular dermis, epidermal thinning, loss of interpapillary ridges, and atrophy of dermal appendages, leading to skin fibrosis, calcinosis, Raynaud's phenomenon, and cutaneous ulcers (the most common cutaneous manifestations of SSc).

Although the major concerns of this condition are the vascular abnormalities and the progressive involvement of the internal organs, the diffuse fibrosis of the skin and joints are the most distinct manifestation of the disease. Skin involvement is almost universally present in patients with SSc and is a useful tool for disease classification. Skin scores also correlate proportionally with disease severity given that patients with extensive cutaneous involvement have a very poor prognosis.[3] In this article, the authors review the management of each one of the skin manifestations seen in SSc from the available conventional agents to the new alternative drugs that are still under study.

## RAYNAUD'S PHENOMENON

Raynaud's phenomenon (RP) was first described by Auguste-Maurice Raynaud in 1862, who described the phenomenon as a change of color, sometimes accompanied

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by pain, of the hands and feet after exposure to cold temperatures or emotional stress.[4] A few decades later, the disease was classified as a primary or idiopathic RP (also known as Raynaud's disease) when it is the sole manifestation in a patient or as a secondary RP when it accompanies other diseases, mainly connective tissue disorders, such as SSc, systemic lupus erythematosus, and Sjogren's syndrome.[5]

Primary RP is seen in 5 to 10 percent of the general population. It usually affects women in the second or third decade of life and sometimes runs in families. It is usually mild and involves fingers and toes symmetrically.[1]

RP is a cardinal feature of SSc and occurs in almost all cases (95%).[1,5] In contrast to primary RP, which is a functional abnormality, secondary RP is a combination of a vasospastic event together with a structural vessel wall abnormality. Associated structural vasculopathy combined with intermittent vasospasm is responsible for the serious digital vascular complications of SSc, including digital ulceration, soft tissue or bone infection, and critical ischemia or gangrene. Many agents have been used for the treatment of RP in patients with systemic sclerosis. Although RP is one of the most important cutaneous signs of SSc, it is in fact a vascular process and will be discussed in another section of this article. Furthermore, similar treatment will be discussed with the management of digital ulceration.

## DIGITAL ULCERS

Digital ulcers (DUs) are a major clinical problem in patients with limited or diffuse SSc, occurring in 30 and 58 percent of patients, respectively. DUs are slightly more common in patients with diffuse SSc; as such, they are considered a marker for disease severity. DUs can appear on the fingers or toes and are located usually on the tips or the finger creases and they are secondary to ischemic tissue injury. Other ulcers frequently develop over bony prominences and are frequently related to repetitive trauma of contractured joints. Ulcerations also frequently develop over areas with calcinosis. DUs are very painful; the healing is slow due to the atrophic, fibrotic, and avascular nature of the local tissue. This results in a functional impairment with a significant impact on the patient's quality of life (physical and psychological). Furthermore, chronic ulcers can become infected, resulting in gangrene, osteomyelitis, and amputation.[6-8]

The etiology of DUs is multifactorial; however, there are two principal problems involved in the appearance of DUs—a vascular wall structural (intima proliferation) and functional (overproduction of vasoconstrictors) abnormalities, and a variable degree of intraluminal thrombosis.

There are several proposed mechanisms for the pathophysiology of the disease and the treatment options had been developed with the specific aim to block these mechanisms. The triggering factors in the development of digital ulcerations are still unknown, but it is believed that smooth muscle cells migrate into the intimal layer of the microvasculature and differentiate into myofibroblasts that secrete collagen and other extracellular matrix. This process leads to a fixed narrowing of the intravascular lumen, which hinders the blood flow and causes chronic tissue ischemia.[8] The endothelial injury is accompanied by increased levels of endothelin-1(ET-1), a potent vasoconstrictor peptide. ET-1 actions are mediated through endothelin type A (ETa) receptors present on vascular smooth-muscle cells and endothelin type B (ETb) receptors present on vascular endothelial and smooth-muscle cells. As activation of ETa receptors leads to vasoconstriction and vascular remodeling, activation of ETb receptors predominantly results in vasodilatation.[9] The excessive production of vasoconstrictors, such as endothelin,[1] results in an underproduction of vasodilators, such as prostacyclin and nitric oxide.[8]

Another proposed mechanism of endothelial injury is the presence of endothelial cell antibodies. The other consequence of this endothelial damage is platelet activation with release of thromboxane, which leads to intraluminal thrombosis.[6-8]

Despite the substantial impact in the quality of life, there are still no guidelines for the treatment of digital ulcers secondary to SSc, and there is a need for systematic research to define new treatments for this complication. When assessing a patient with a DU, there are a number of indicators to determine severity and assist in management—DU size, number, location, loss of function, pain, and tissue loss are all important. A very large ulcer may be associated with longer healing time, pulp loss, increased risk of infection, and pain. There is more risk for severity in patients with multiple ulcers.[7]

**Nonpharmacological treatment**. The first approach in the treatment is to help patients deal with the pain associated with DUs since this has a considerable impact on quality of life. It is also important to restore hand function, improve digital circulation, prevent infection, promote healing, and avoid the formation of new ulcers. Attention to these issues will reduce the need for surgical procedures, such as amputation. It is important to have good skin care and to minimize the occurrence of minor trauma. Vasoconstriction can be reduced by avoiding precipitating factors, such as cold, stress, and nicotine. The use of topical antibiotics and occlusive dressings (hydrocolloid) can promote healing, but the choice of dressings depends on the presence or absence of underlying infection.[6,9]

*Pain medication.* Pain related to DU is exquisite and may last as long as the DU is active, which could range from months to years. Treatment of the pain should be instituted promptly and adequately escalated. Although the nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently prescribed, they should be avoided in favor of acetaminophen or opiates since NSAIDs have a risk of gastrointestinal disease and renal toxicity.[8,9]

*Infection.* Control of the colonization and contamination is crucial to prevent further tissue loss. It is important to perform a skin culture before starting antibiotic therapy.

Infected DUs require prompt treatment with oral antibiotics (depending on culture results) for prolonged periods of time. In some cases, parenteral administration of the antibiotic therapy may be warranted. For DUs located over bony prominences, radiographic assessment for osteomyelitis should be performed. Although plain radiographs may be ordered first, the preferred technique is a magnetic resonance imaging (MRI) because of its high sensitivity in the detection of bone marrow changes.[6,7,9]

**Pharmacological treatment.** *Dihydropyridine-type calcium antagonist.* Nifedipine and nicardipine, usually oral, should be considered as the first-line therapy for Raynaud's phenomenon (RP), as the recently published European League Against Rheumatism (EULAR) recommendations for the treatment of systemic sclerosis suggests. These agents have the potential to reduce the risk of ulcers developing. However, there is limited data to support the use of calcium channel blockers in the treatment of DUs once they have developed.[10]

*Prostacyclin analogues.* Iloprost has become the standard of care for patients with severe SSc-related digital vasculopathy and DU and it should be considered for first-line therapy in the treatment of DU.[7]

The prostacyclins currently available are iloprost and epoprostenol, which are both administered intravenously and used to promote primary healing of the ulcers. Prostacyclin improves the DU by acting as a potent vasodilator and actively inhibits platelet aggregation. A study using intravenous infusions of iloprost for 5 to 8 hours for 3 to 5 consecutive days at doses of up to 2ng/kg/minute resulted in reductions in frequency, duration and severity of RP attacks, and the formation of new DUs. There was also evidence of healing of pre-existing DUs. This study also showed an impressive persistent beneficial effect after nine weeks of therapy compared to placebo.[7,9]

*Oral endothelin receptor blockers (bosentan, sitaxentan, and ambrisentan).* Bosentan should be considered in diffuse SSc with multiple digital ulcers after failure of calcium antagonists, as the recently published EULAR recommendations for the treatment of systemic sclerosis suggest. Endothelin-1 is elevated in the serum of patients with SSc, especially in those with DUs and co-segregates as a biomarker of vascular severity, much as it does in patients with pulmonary hypertension.[7]

There have been two separate trials using bosentan for the management of DUs. RAPIDS-1—a 16-week, randomized, double-blind, multicenter study administering bosentan 62.5mg twice daily titrated up to 125mg twice daily after one month—was effective at preventing new DUs in patients with SSc (significant 48% reduction). There was also improvement of hand function, but there was no effect on the healing of existing ulcers. RAPIDS-2 was a 24-week, randomized, double-blind, multicenter study, with bosentan 62.5mg twice daily for four weeks and then titrated to 125mg twice daily for 20 weeks. Bosentan was associated with a significant reduction in number of new ulcers (30% fewer), and effects were apparently noted as early as 12 weeks. The reduction was particularly observed in patients with more than three active DUs at baseline. As in RAPIDS-1, there was also no effect on actual healing, but it is evident that perhaps bosentan can be used as a prophylactic treatment of new ulcers.[7]

There is also a case report with the use of a selective endothelin type A receptor antagonist (sitaxentan) 100mg daily. After two months of treatment, the patient reported improvement of the pain and after four months, the patient's digital ulcers had nearly completely healed.[7]

However, reported cases of hepatotoxicity as a frequent side effect had been reported with sitaxentan. Seven cases of severe hepatitis-like drug reactions and two additional cases of fatal liver injury have been described in association with sitaxentan. In all of these cases, liver function deteriorated despite discontinuation of the drug. To date, there are no reports of this hepatic complication related to ambrisentan and bosentan. In contrast, four deaths and one case of liver transplantation related to the use of sitaxentan have been reported among the 2,000 patients treated worldwide. However, a warning label has been added to the United States prescriber information of bosentan, mentioning rare cases of liver failure in patients treated with bosentan. It had been suggested that there are at least two types of liver injury associated with the use of the endotelin receptors antagonist, one toxic dose dependent and reversible after dose reduction or discontinuation of the drug, and another, which is possibly idiosyncratic or immunologically mediated. The recent report of the two additional cases of fatal liver injury related to the use of sitaxentan in pulmonary arterial hypertension patients enrolled in a randomized, controlled study has prompted the voluntary discontinuation of all ongoing clinical trials with this compound and the withdrawal of the commercial drug (Thelin, 100mg sitaxentan tablets) from the market worldwide.[11]

*Angiotensin converting enzyme inhibitors and alpha adrenergic blockers.* Several studies have shown that these medications also improved RP and DUs, but recently a randomized double-blind, placebo-controlled trial had failed to show efficacy in this setting.[7]

*Nitrates.* Topical, sublingual, or oral formulations are sometimes used as adjunctive therapy in the treatment of RP and DUs, but no randomized, controlled studies have been published evaluating the effects on DUs healing.[9]

*Phosphodiesterase inhibitors.* Sildenafil has been shown to benefit patients with the RP episodes, but data related to its effects on DUs is very limited. A recent double-blind, placebo-controlled study involving 57 patients with RP secondary to SSc comparing sildenafil 200 mg/day versus placebo demonstrated a reduction in the frequency of attacks of RP in the sildenafil group, although the result was not statistically significant.[12] There is a need for more prospective studies on these types of agents in DUs.[7]

*Statins.* Oral atorvastatin administration 40mg/day in patients with SSc resulted in a significant improvement in endothelial dysfunction, which may be attributed to their anti-inflammatory and immunomodulatory properties. Furthermore, studies showed that levels of nitric oxide

increased and levels of endothelin-1 decreased after atorvastatin therapy compared to the placebo group.[13]

**Surgery.** Surgical procedures may be required for severe DUs and the treatments most commonly described in the literature are microsurgical revascularization of the hand, digital arterial reconstruction, and peripheral or digital sympathectomy, which have been reported to improve healing of DUs within 4 to 6 weeks. These procedures should be used as a last resort, as they are invasive and recurrence of DUs can occur in up to one-third of patients.[9]

Vascular reconstruction in patients with refractory digital ulcers or gangrene is a procedure used in SSc patients because the arterial occlusion frequently involves the ulnar and digital arteries, and the intervention can restore digital perfusion. Some authors have demonstrated that cervical sympathectomy can treat the symptoms of pain, but did not promote the healing of established DUs nor prevent the formation of new ulcers. Several studies have showed that digital sympathectomy allows healing by increasing nutritional blood flow to the affected digits. Although these results showed short-term follow-up data that were encouraging, longer follow-up data were not presented.

In conclusion, digital sympathectomy can be an option in patients where the conservative therapies have failed, but it is important to recognize that there are reports of DU recurrences as a result of disease progression. Digital pain is the most incapacitating symptom and ulnar and median nerve blocks at the wrist level with xylocaine or marcaine have shown some improvement. Other authors have concluded that conservative fingertip amputation is the treatment of choice for nonhealing digital ulcers.[14,15]

## SKIN FIBROSIS

Skin thickening is an important manifestation of systemic sclerosis, with only two percent of patients not reporting this sign. Although there are no specific strategies for treatment, many strategies have been tried.

In most studies, skin thickness was evaluated using the modified Rodnan skin score, in which the skin thickening is assessed by palpation of the skin in 17 areas of the body (fingers, hands, forearms, arms, feet, legs and thighs, face, chest, and abdomen) using a 0 to 3 scale, where 0=normal, 1=mild thickness, 2=moderate thickness, and 3=severe thickness. Total skin score (TSS) can range from 0 (no thickening) to 51 (severe thickening in all 17 areas).

**Nonpharmacological treatment.** Patient education and rehabilitation techniques, such as stretching, improvement of range of motion, heat, massage, and splints may contribute to the management of SSc. Of those, range-of-motion exercises, heat, and connective tissue massage with joint manipulation to the hands can improve range of motion. Other techniques have not been well-studied or were not effective.[16]

**Pharmacological treatment.** *Corticosteroids.* Corticosteroids have been traditionally used in the treatment of SSc. However, corticosteroid use has been associated with the development of renal crisis.[17] A study comparing dexamethasone 100mg pulse therapy once a month for six months versus placebo demonstrated an improvement in the average TSS of the dexamethasone group and deterioration in the score of the placebo group.[18] Another study confirmed the histopathological improvement with the use of this therapy.[19] Although there are no hard data to advocate corticosteroid use for skin fibrosis, most specialists recommend its use for the treatment of other complication of SSc, such as myositis and alveolitis.

*D-penicillamine.* Penicillamine is a metabolite of penicillin with no antibiotic activity; it works by reducing the number of T-lymphocytes and preventing collagen formation by blocking aldehyde groups involved in the inter- and intramolecular cross linkage of mature collagen. It also accelerates the turnover of insoluble collagen by cleaving intermolecular bonds that stabilize the fibrous structure. This drug also inhibits macrophage function by decreasing interleukin-1 (IL-1) production. It has shown to improve the overall prognosis of the disease by reducing the skin sclerosis and avoiding further visceral involvement. In a 15-month prospective study, where 60 patients were given 750mg/day of D-penicillamine for at least six months, there was significant reduction of sclerotic skin, with less progression in renal and pulmonary involvement.[20]

Furthermore, the rapid recurrence of active disease in patients who discontinued D-penicillamine supports the beneficial therapeutic effect of the agent.[21] However, there have been several reports of adverse effects associated with D-penicillamine therapy for systemic sclerosis, including cutaneous drug reaction and pruritus (the most common),[22] pemphigus vulgaris,[23] myasthenia gravis,[24] lupus erythematosus-like eruption,[25] polymyositis,[26] Grover's disease,[27] polymyositis,[28] obliterating bronchiolitis,[29] Goodpasture-like syndrome,[30] lipoid nephrosis,[31] extracapillary glomerulonephritis,[32] taste dysfunction with changes in zinc and copper metabolism,[33] and immune thrombocytopenia.[34] A recent study involving 84 patients with progressive, diffuse cutaneous systemic sclerosis of recent onset suggests that D-penicillamine at a median dose of 750mg/day still plays a role in the treatment of this specific selected cohort of patients with a statistically significant reduction in skin involvement as well as improvement of renal, cardiac, and pulmonary involvement.[35]

*Cyclosporine A (CSA).* Cyclosporine A is a member of the family of immunophilins-proteins that block the dephosphorylation of the nuclear factor of activated T cells (NFATc)—a transcription factor for inflammatory cytokines, such as IL-2, which, when inhibited, results in a reduction of the number of CD4+ and CD8+ T cells in the skin. Significant decrease in skin thickening has been reported in patients treated in a CSA, 48-week, open study, but avoidance of progression in pulmonary and cardiac involvement was not noted.[36] Many anecdotes and several small series studying the effectiveness of CSA in SSc have been reported, some of them with long-term control of the disease on relative low doses (CSA 2mg/kg). Even though

long-term CSA treatment is not considered standard therapy because of the increased risk of side effects, such as hypertension and renal crisis,[37,38] some authors consider CSA a possible option in carefully selected cases.[39]

*Methotrexate (MTX).* Methotrexate is a folic acid analogue that competitively inhibits dihydrofolate reductase (DHFR), an enzyme that converts dihydrofolate to tetrahydrofolate, a necessary cofactor in the synthesis of thymidylate and purine nucleotides. Although the use of MTX in the treatment of SSc remains controversial, several placebo-controlled studies have been undertaken to determine the effectiveness of MTX in SSc. In some of these studies, no statistically significant difference was noted in any group and a higher rate of side effects was reported in the MTX group.[40,41] Another study has found a significant difference ($P$=0.03) in terms of TSS at Week 24 comparing MTX with placebo.[42] There are also some reports of good response in skin scores after MTX, significant worsening after stopping, and subsequent improvement with reinstitution of MTX suggesting its efficacy.[43]

*Azathioprine.* Converted to 6-mercaptopurine (6-MP) after absorption, azathioprine is a purine analogue that incorporates into deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) and inhibits purine metabolism and cell division. It has been subjectively helpful in some cases. Relapse of skin involvement occurs after discontinuation of therapy, further suggesting a beneficial effect.[44]

*Chlorambucil.* Chlorambucil is an alkylating agent derived from nitrogen mustard, which cross-links DNA. It has been shown to decrease the TSS in SSc patients in trial versus placebo.[45] However, another randomized, double-blind, parallel study of 65 patients comparing placebo and chlorambucil (0.05–0.1mg/kg/day) showed more complications in the chlorambucil group, but failed to show significant differences between the treatment groups.[46]

*5-Fluorouracil (5-FU).* 5-FU is a pyrimidine analog and works through irreversible inhibition of thymidylate synthase. 5-FU was proven useful in 12 patients treated (10–20mg/kg/week) for 1.5 to 20 months. All patients showed significant ($p$<0.05) improvement in the TSS.[47]

*Cyclophosphamide.* Cyclophosphamide is a nitrogen mustard alkylating agent used to treat various types of cancer and some autoimmune disorders. It has been extensively studied for the treatment of SSc-related lung disease. Furthermore, cyclophosphamide also demonstrated improvement of the skin involvement after one year of treatment with 1 to 2mg/kg/day.[48] However, the use of cyclophosphamide for the treatment of SSc without internal organ involvement is questionable.

*Gamma-interferon.* Gamma-interferon (IFN) is a potent and selective inhibitor of fibroblast proliferation and collagen production by human dermal fibroblasts *in vitro*. It has shown activity in cultures of fibroblasts from SSc patients by inhibition of collagen retraction, reduction of synthesis of collagen, and noncollagen proteins. It decreases messenger RNA coding for pro alpha 1 collagen and inhibits glycosaminoglycan synthesis.[49] It has proven useful, showing significant improvement during a 12-month trial of the TSS in nine patients who received 50µg/day, 3 days/week.[50] However, it failed to show effectiveness in SSc in a randomized, controlled, multicenter trial[51] and other prospective studies.[52,53]

*Alpha IFN-2a.* Alpha IFN-2a binds to specific membrane receptors inducing certain enzymes, suppresses cellular proliferation, and inhibits viral replication. It has failed to show effectiveness in the treatment of SSc in a randomized, double-blind, placebo-controlled trial on 35 patients. However, it was found to be associated with a greater deterioration in lung function in patients receiving active therapy.[54]

*Calcitriol (1,25 dihydroxycholecalciferol).* This is the naturally occurring form of activated vitamin D. Calcitriol (0.75µg/day for 6 months, followed by 1.25µg /day for 3 months) failed to show significant difference in terms of TSS in a randomized, double-blind, placebo-controlled study of nine months' duration in seven patients with SSc. Conclusions are hard to draw because of the small number of patients enrolled.[55]

*Retinoids.* Retinoids are structural and functional analogues of vitamin A that act on cellular differentiation and proliferation. Etetrinate, a vitamin A derivative was studied on 31 SSc patients alone and in combination with other therapeutic agents, such as systemic corticosteroids, immunosuppressants, D-penicillamine, MTX, bucillamine, and ultraviolet light A (UVA) irradiation. The results reached statistically significant improvement ($P$<0.01) for all patients taking etetrinate.[56] Systemic isotretinoin has also been used in the treatment of SSc with improvement of cutaneous lesions, but with no effect on internal organs.[57] Topical tocoretinate has also been used for the treatment of SSc, where it proved to clinically and histologically improve SSc lesions.[58]

*Relaxin.* This peptide hormone of the insulin super family is involved in the promotion of extracellular matrix remodeling. It has shown efficacy in the prevention and treatment of experimentally induced fibrosis in a variety of models. Relaxin treatment of normal dermal fibroblasts or scleroderma fibroblasts resulted in a marked decrease in collagen secretion and increased collagen degradation. Preliminary studies on 30 patients with stable diffuse scleroderma of moderate severity showed relaxin to be safe and well-tolerated, but minor changes in skin scores were reported.[59] More recently, a placebo-controlled trial using two different doses (25 and 100µg/kg/day) of relaxin showed the lower dose to induce significant improvement in skin thickness. However, at the higher dose, no benefit was seen.[60] In a subsequent study, these results were not replicated, and the lower dose of relaxin was no different from placebo. In addition, serious renal adverse events, such as increase of serum creatinine, renal crisis, or hypertension, were related to relaxin after stopping the infusion.[61,62]

*Intravenous immunoglobulin (IVIg).* Based on the autoimmune nature of SSc, intravenous immunoglobulin (IVIg ) has been postulated as a potential useful treatment. Based on this theory, a series of three patients who received

six monthly courses of high-dose IVIg (2g/kg) with a decrease in their TSS was published. Due to the small sample size and the lack of statistical analysis, these results should be carefully interpreted.[63] Another open-label study was performed using the same regimen on 15 patients reaching significant reduction in the TSS ($P$<0.001) after treatment.[64]

*Extracorporeal photochemotherapy (EP).* EP administered in two consecutive days monthly was compared to D-penicillamine (750mg/d) in a randomized, parallel-group, single-blinded clinical trial on 79 patients with systemic sclerosis of recent onset. In this study, extracorporeal photochemotherapy showed significant higher improvement in skin severity score ($p$=0.02). The mean skin severity score, mean percent skin involvement, and mean oral aperture measurements were significantly improved at six months in extracorporeal photochemotherapy patients. In this study, it was not until the tenth month when D-penicillamine patients showed improvement in mean skin severity score and mean percent skin involvement. Higher adverse events were also found in those taking D-penicillamine.[65] These results were confirmed in another randomized, double-blind, placebo-controlled clinical trial on four patients, resulting in significant improvement in skin scores as compared with baseline. This was observed at six months ($P$=0.0024) and 12 months ($P$=0.008). However, comparison of skin scores between the two study arms did not achieve statistical significance,[66] and therefore some authors do not consider long-term SSc to be sufficiently controlled by photopheresis alone.[67]

*Factor XIII (FXIII).* Factor XIII's function is to cross-link fibrin and protect it from the fibrinolytic activity of plasmin. It has shown to reduce synthesis of collagen in SSc fibroblasts to a level similar to that of normal fibroblasts by reducing collagen synthesis and increasing degradation of the newly synthesized collagen.[68] A double-blind, randomized, cross-over study of patients receiving FXIII, showed improvement in 50 percent of the patients treated. However, cutaneous improvement was the only beneficial effect of this therapy.[69]

*Anti-TNF therapy.* Recently, various studies have evaluated the efficacy of anti-TNF drugs in SSc. Both, etanercept and infliximab have shown efficacy in the treatment of inflammatory arthritis associated with SSc; however, the effect on skin score is uncertain.[70]

*Imatinib.* Potential use of this drug as an inhibitor of fibrosis has been postulated. It functions as a specific inhibitor of a number of tyrosine kinase enzymes, such as the transforming growth factor beta (TGFβ) and platelet-derived growth factor (PDGF) pathways. It has been shown to reduce basal synthesis of COL1A1, COL1A2, and fibronectin 1 messenger RNA in SSc and normal dermal fibroblasts in a dose-dependent manner on a bleomycin-induced experimental dermal fibrosis.[71] These results led to a preclinical study that showed imatinib to inhibit the proliferation of normal dermal and scleroderma fibroblasts.[72] Several recent clinical trials have been showing the efficacy of imatinib for the treatment of SSc, achieving improvement not only in skin thickening, but also in pulmonary function test. However, further double-blind, randomized, placebo-controlled trials are needed.[73–76]

*Rituximab.* Rituximab is a chimeric monoclonal antibody that inhibits CD20-mediated B-cell proliferation and differentiation. Recently, a number of case reports and noncontrolled clinical trials suggested that rituximab may be effective for the treatment of SSc showing significant improvement in skin scores and lung function. However, similar to the other biological treatments, further double-blind, randomized, placebo-controlled trials are needed to confirm these results.[77–79]

**TABLE 1. Other therapies for skin fibrosis**

| REFERENCE | DRUG | DOSE | NUMBER OF PATIENTS | RESULTS |
|---|---|---|---|---|
| Sakakibara N et al[81] | UVA1, 340–400nm and PUVA therapy | — | 3 | Histological improvement |
| De Souza RB et al[82] | Pentoxyphylline/vitamin E | 800mg/800UI qd | 12 | Significant reduction of the TSS |
| Barr PO et al[83] | Hyperbaric oxygen | — | 1 | Regression of skin contraction and ulcer healing |
| Zarafonetis CJ et al[84] | Potassium para-aminobenzoate | 12–12.5g/qd | 224 | Significant reduction of the TSS |
| Clegg DO et al[85] | Potassium para-aminobenzoate | 12 g/qd | 146 | No significant reduction of the TSS |
| Nash RA et al[86] | Allogeneic hematopoietic cell transplantation | — | 2 | Improvement in 1 of 2 patients |

Many other preparations, including ketotifen,[87] disodium EDTA, glyceryl trinitrate,[88] phenformin and ethyloestrenol,[89] dihydrotachysterol, salazopyrin,[90] or infliximab[91] have not proved beneficial.
UVA=ultraviolet light A; PUVA=psoralen + ultraviolet light; TSS=total skin score

**Surgery.** Surgical treatment also plays a role in the management of SSc. Surgical procedures, such as arthroplasty, arthrodeses, excision of painful calcinosis, and digital sympathectomy have shown efficacy in the management of complications of SSc.[80]

## CALCINOSIS

The abnormal deposition of calcium in soft tissues independent of the levels of calcium and phosphorous in the serum is a frequent finding in systemic sclerosis and other autoimmune-inflammatory diseases. Dystrophic calcification of acral distribution (digits, elbows, knees) is the most common type of calcinosis associated to SSc.[92,93] It occurs in approximately 25 percent of patients with systemic sclerosis[94] causing pain, local inflammation, irritation, muscle atrophy, ulceration with the possibility of secondary infection, and joint contractures. The process often leads to severe disability and increased morbidity. Although many hypotheses exist attempting to explain the presence of calcinosis in the setting of SSc, the pathophysiological mechanism responsible for its development is still unclear. Few therapies have shown to be effective for the long-term management of this condition. Some treatments used with variable results include coumadin, colchicine, biphosphonates, diltiazem, minocycline, aluminum hydroxide, surgical excision, and $CO_2$ laser. New possible therapeutic modalities have arisen from recent clinical trials, namely IVIg, extracorporeal shock wave lithotripsy, fetuin-A (α-2-Heremans-Schmid glycoprotein, AHSG), and a topical preparation of myo-inositol hexaphosphate (InsP6, phytate).

**Pharmacological treatment.** *Warfarin.* Berger et al[95] reported that low doses of warfarin (1mg/day) for 18 months had beneficial effects in patients suffering from calcinosis cutis in the setting of both dermatomyositis and systemic sclerosis. In this report, they also hypothesized that warfarin helped decrease the appearance of calcinosis since it inhibits the carboxylation of glutamine, therefore inhibiting the formation of γ-carboxyglutamic acid, an amino acid that is present in high concentration in calcinotic plaques. Years later, Yoshida and Torikai[96] described a good response of one patient with the same therapeutic regimen. More recently, Cukierman et al[97] also reported the use of warfarin. Two of the three patients who presented with newer and smaller calcified plaques responded with reduced lesion size after one year of treatment, but, in contrast, the one patient whose lesions were older and larger did not respond and the plaques remained unchanged. Therefore, this drug seems to be an option in patients with new onset calcinosis. None of these groups reported increased tendency for bleeding or alterations of the coagulation times with these low doses of anticoagulants.[95–97]

*Aluminum hydroxide.* This antacid binds to phosphate and reduces plasma calcium phosphate by minimizing its absorption in the gastrointestinal tract. Its strength lays in its lack of adverse effects, although constipation can occur.[98] Reports of its efficacy are usually in combination with other drugs.

*Minocycline.* This tetracycline derivative has been widely used in dermatology for its antibiotic and anti-inflammatory properties. In the case of calcinosis cutis, the rationale behind the use of minocycline is its capacity to affect osteoclastic function by chelating calcium. In addition it produces inhibition of collagenases and neutrophil matrix metalloproteinases (MMP) *in vitro*. On the other hand, since calcinotic plaques are often ulcerated, the antibiotic activity of this drug may also contribute to the improvement of the lesions. In a report by Robertson et al,[94] nine patients with limited SSc were treated with 50 to 100mg of minocycline daily for a mean of 3.5 years. The inflammation, appearance of ulceration, and discomfort associated with the lesions decreased considerably in eight patients. Plaque size also decreased, although this occurred very slowly. The improvement was evident for the majority of patients after 4.8 months. They also proposed that it was beneficial to have cyclic treatments of 4 to 8 weeks when the patient starts noticing a flare instead of continuous treatment. A blue-black discoloration of the calcium plaques and dose-dependent dizziness were noted during treatment, but treatment was well-tolerated otherwise.

*Diltiazem.* Although the use of this calcium channel blocker for Raynaud's phenomenom has been widely documented, few reports of calcinosis treated with this agent exist in the literature. Use of diltiazem for calcinosis appears to have a different mechanism of action. Since it reduces the intracellular flow of calcium ions and it helps to correct the hypothesized calcium disorder of the connective tissues, it therefore inhibits further calcium deposition in the soft tissues. **[[AUTHOR: last two sentences correct as edited?]]**

Twelve patients with SSc-associated calcinosis were treated with diltiazem 180mg daily in a study by Vayssairat et al.[99] Only three patients showed slight radiological signs of improvement. Other trials where higher doses were used (240 vs. 480mg daily) reported better results, which may suggest the effects may be dose-dependent. A recent interesting report of success was the case of a young SSc patient treated with a total of 90mg of diltiazem three times a day in combination with aluminum (830mg)/magnesium hydroxide (185mg) 15mL three times a day. Improvement was noticed after two months, and after one year, the size and induration of the calcified plaques had reduced significantly. After the sixth year of treatment, the lesions almost entirely disappeared.[100]

*Intravenous immunoglobulin (IVIg).* IVIg is a plasma product derived by a collection of antibodies that have proven effective in the treatment of several immune system disorders. Based on reports where dermatomyositis-associated calcinosis was treated successfully with IVIg, Schanz et al[92] treated one CREST syndrome patient with 2g/kg IVIg in a four-day protocol once a month. Lesions markedly improved after the third cycle of treatment; nevertheless, lesions recurred six months after IVIg discontinuation. Another study by Kalajian et al[101] did not report the same positive results.

*Fetuin-A (α-2-Heremans-Schmid glycoprotein,*

*AHSG).* This glycoprotein seems to have an important role in the inhibition of calcification as suggested by a study where serum levels were measured in 41 patients with SSc. The levels of fetuin-A were lower in the 20 patients who presented with calcinosis and were even lower in patients with anticentromere antibodies. Lower levels of this protein were also found in patients with vascular abnormalities.[102] These observations and further investigation may lead to the use of AHSG to treat calcinosis and other vascular complications in the future.

*Myo-inositol hexaphosphate (InsP6, phytate).* This diet-dependent molecule, which is ubiquitously found in plant seeds and in the body fluid and tissues of mammals, is a potent inhibitor of calcium salts crystallization. An experiment was conducted where seven rats with artificially created calcinosis plaques were treated with a cream containing InsP6 and compared with seven rats in a control group.

This molecule was absorbed through the skin and demonstrated a decrease in the weight and size of the calcium deposition. Further investigation is needed to determine if these positive results are applicable to humans.[103]

*Colchicine, probenecid, intralesional steroids, anti-TNF, and biophoshonate.* Anecdotal use of these agents has not shown benefit.

**Nonpharmacological treatment.** *Extracorporeal shock wave lithotripsy (ESWL).* This minimally invasive procedure, in which a high-intensity acoustic pulse breaks a calculus, was used successfully in one patient with recalcitrant dystrophic calcinosis of the legs in the setting of CREST syndrome. Fifteen days after the first session, pain and ulceration diminished considerably. After two more treatments, the patient was free of calcifications when assessed radiologically.

This technique provides precise ablation of the lesions and prevented damage of the unaffected tissue.[93] Chan and Li[104] also reported successful treatment of calcinosis associated to dermatomyositis with ESWL. There have been reports where this technique failed to show efficacy.

*Carbon dioxide laser.* Laser vaporization offers some advantages over surgical excision. It allows the precise ablation of the lesions, saving the patient damage to the adjacent healthy tissue. There is also less bleeding and less postprocedure discomfort. To our knowledge, there has only been two reports of successful use of this technique for the treatment of calcinosis.[105,106]

**Surgery.** This treatment modality is usually the last resort after multiple medical failures, or a quick fix for pain control of well-demarcated and localized lesions. This procedure requires both operative and postoperative anesthesia. The main disadvantage of this invasive approach is the possibility of damaging healthy tissue and/or producing further ischemia by compromising the neurovascular network.[107]

## CONCLUSION

Optimal treatment of systemic sclerosis (SSc) is a challenge because the pathogenesis of SSc is unclear and it is an uncommon and clinically heterogeneous disease affecting multiple organ systems. Therefore, the emphasis is often made to manage symptoms and complications. No treatment is available that completely halts the natural progression of the disease and the incidence of recurrence is extremely high even in patients with an initially positive response to the available treatments. Consequently, efforts are being made to study the disease in its early stages before overt disease and irreversible organ damage have occurred. Early diagnosis of SSc could enable the early start of treatment, which could slow disease progression and the appearance of clinical complications. Although there is no cure for systemic sclerosis, management of its associated complications can help improve patients' quality of life. Furthermore, new treatments that may target specific organ/tissue damage associated with SSc are in development and show promising results.

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